REMARKS

These remarks are in response to the Office Action mailed October 18, 2006 ("the Office Action"). Claims 1-3, 5-9, 11, 12, and 21 have been amended. Claim 1 has been amended to specify that the bone condition is "associated with excessive resorption or breakdown of bone tissue." Support for this amendment is found in the specification, e.g., at page 2, lines 9-10. Claims 1, 7, and 21 have been amended to delete the term "FGF-8 analog" and to require that the FGF-8 agonist recited in the claim include "an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, 2, or 3, or a fragment thereof comprising at least 10 amino acids of the sequence." This amendment is supported, e.g., at page 5, lines 10-22, of the specification. Claims 1, 7, and 21 have been amended to state that the FGF-8 or FGF-8 agonist is administered in an amount effective to treat the condition recited in the preamble of the claim. Support for this amendment is found in the specification, e.g., at page 8, lines 17-26. Claims 5 and 11 have been amended to recite 95% identity rather than 60% identity. Support for this amendment is found, e.g., at page 5, lines 20-23. New claims 23-27 mirror claims 2-6 and depend, directly or indirectly, from claim 21. The other amendments to dependent claims 2, 3, 5, 6, 8, 9, 11, and 12 are for clarity.

Claims 13-18 have been canceled. No new matter has been added. Claims 1-12, 21, and 23-27 are under examination.

Reconsideration of the claims, as amended, is respectfully requested in view of the following remarks.

Claim Objections

Claims 1-18 and 21 were objected to because they recite non-elected species (e.g., SEQ ID NOs.:1 and 2). It is noted that, upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim. MPEP § 809.02(a).

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-18 and 21 were rejected as indefinite. The Office Action stated that "[t]he claims do not recite what an effective amount of FGF-8, FGF-8 analog or FGF-8 agonist is effective to do...Note that amending the claims to recite what the effective amount of FGF-8, FGF-8 analog, or FGF-8 agonist is effective to do would obviate this rejection" (carryover paragraph, pages 2-3).

This rejection has been met by the amendment of the claims. Claims 1, 7, and 21, as amended, state that the FGF-8 or FGF-8 agonist is administered in an amount effective to "treat the bone condition", "increase or maintain bone density", and "treat the osteoporosis, osteopenia, bone defects, or osteogenesis imperfecta", respectively. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-18 and 21 were rejected as lacking enablement.

First, the Office Action stated that "with respect to claim 1-6, the term 'bone condition' is extremely broad and encompasses conditions such as acromegaly or osteosclerotic bone metastasis (in certain cancer), both of which are characterized by too much bone formation" (page 4). This ground for rejection has been met by the amendment of claim 1 to recite a method for treating a bone condition "associated with excessive resorption or breakdown of bone tissue." On page 3, the Office Action acknowledged that the specification is enablement for treating a bone condition characterized by too little bone formation or for increasing or maintaining bone density.

Next, the Office Action stated that

> with respect to all of the claims, there are issues of breadth, complexity, predictability, direction provided by the inventor and existence of working examples concerning the recitation [sic, of] the FGF-8, FGF-8 variants, fragments, analogs, or agonists. Evidence as to why the claims as broadly recited are not enabled can be found in Blunt et al...Applicants found that there was a dose dependent increase in osteoblasts (and decrease in osteoclasts) with administration of the FGF-8a isoform, thus while that may provide sufficient evidence that the FGF-8a isoform is enabled, it does not provide any support for

all FGF-8 variants, fragments, analogs or agonists. In addition claims reciting agonists in terms of 60% sequence identity...it is noted that according to Yao et al...that FGF-13 is 70% homologous to FGF-8, thus the broad claims encompass other FGFs altogether. Finally, the term "agonist" encompasses small organic molecules, DNA, as well as unrelated proteins (pages 4-5).

The claims, as amended, recite methods of using FGF-8 and FGF-8 agonists, wherein the FGF-8 agonist comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, 2, or 3, or a fragment thereof, wherein the fragment thereof comprises at least 10 amino acids of the sequence. Thus, the comments in the Office Action regarding 60% sequence identity and "agonists" are not applicable to the amended claims, which are limited to uses of FGF-8 and FGF-8 agonists which have defined structural features.

Blunt et al., *J. Biol. Chem.*, 272(6): 3733-3738, 1997 ("Blunt") was cited in the Office Action as evidence of lack of enablement for FGF-8 variants. Blunt does not report the effects of FGF-8 or FGF-8 variants on osteoblasts or osteoclasts. Blunt describes mitogenic effects of different FGF-8 isoforms on BaF3 cells, which are cells of a pro-B cell line. Blunt's study did not investigate whether different forms of FGF-8 modulate cells involved in bone growth and resorption. Therefore, Blunt's results fail to provide any evidence regarding the enablement of the present claims.

The Office Action also stated:

> In general, with regard to FGF-8, FGF-8 variants, fragments, analogs or agonists, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein fragment or variant is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited...Although the specification outlines art-recognized procedures for producing and screening for active muteins this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be action, which conformation is depending upon surrounding residues, therefore substitution of non-essential

> residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:122-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Furthermore, because there is no functional [sic] on the FGF-8, FGF-8 analog or FGF-8 agonist recited in the claims, the claims encompass administration of non-functional agents for "bone conditions" or "increasing or maintaining bone density" or "stimulating osteoblast growth or modulating osteoblast apoptosis" (pages 6-7).

The Office Action acknowledges that the specification outlines means for making and screening for active muteins, yet it concludes that this guidance is inadequate. Applicants respectfully traverse this part of the rejection. None of the above-quoted remarks in the Office Action indicate why one would not be able to make and use FGF-8 and the FGF-8 agonists recited in the present claims. The references cited in the passage describe challenges in assigning function to sequences discovered in the course of genome sequencing. Applicants claim methods for using FGF-8 and FGF-8 agonists which have a high degree of homology to FGF-8 and fragments thereof. The difficulties in function prediction described in the cited papers are not applicable to the present claims, for example, because the basis for using FGF-8 and FGF-8 agonists is not mere function prediction. Rather, Applicants have provided functional data showing biological effects on osteoblast proliferation and inhibition of osteoclast formation. Screening an agonist would be routine in view of the guidance provided in the specification and the teachings of the art. The experimentation required to show that untested species are effective is not undue.

In the next part of the rejection, it states that claim 13 is not enabled for "modulating" apoptosis (page 7). Claim 13 has been cancelled without prejudice. Therefore, this part of the rejection is met.

In the next part of the rejection, it states:

> Finally, claim 21 is drawn to "preventing osteoporosis, osteopenia, bone defects or osteogenesis imperfecta" in the alternative. The plain English meaning of the word prevention implies 100% success at stopping an event from occurring. The claimed methods do not achieve this goal. Therapeutics inhibit symptoms,

> mechanism and/or the onset of disease, but do not prevent all pathological events from occurring. The use of the word "preventing in the claims implies that not a single adverse even [sic, event] will occur (page 7).

Although Applicants disagree with the Examiner's statement that "preventing" requires 100% success at stopping every single adverse event, claim 21 has been amended to delete the term. Claim 21, as amended, recites a method of treating osteoporosis, osteopenia, bone defects, or osteogenesis imperfecta. It is noted that "treating" includes administration of a compound to a patient, who has, or is determined to have, a bone condition, a symptom of a bone condition, a disease or disorder secondary to a bone condition, or a predisposition toward a bone condition, with the purpose to cure, alleviate, relieve, remedy, or ameliorate the bone condition, the symptom of the bone condition, the disease or disorder secondary to the bone condition, or the predisposition toward the bone condition (specification, page 8, lines 10-16).

In view of the foregoing, Applicants respectfully request withdrawal of the rejections of claims 1-12[1] and 21 as lacking enablement.

Rejections under 35 U.S.C. § 102

Singh et al., WO 01/006622

Claims 1-18 and 21 were rejected under § 102(b) as anticipated by Singh et al., WO 01/006622 ("Singh"). The Office Action stated:

> The claims recite a method of treating a bone condition or a method for increasing or maintaining bone density or a method for stimulating osteoblast growth or modulating osteoblast apoptosis comprising administering to a patient in need thereof an effective amount of FGF-8, FGF-8 analog, or a FGF-8 agonist…Note that the claims do not recite what an effective amount…is effective to do, thus for the purpose of prior art, the claims encompass administration of FGF-8, FGF-8 analog or FGF-8 agonist to anybody or anything for any purpose.
>
> Singh et al. teach a method of administering an FGF-8 compound with 100% sequence identity (see Appendix 1) to SEQ ID NO:3 of the instant application, or fragments thereof or variants having at least 90% sequence identity for the purpose of treating neurological disorders…In addition, at p. 8 (last paragraph) to p. 9 (1^{st} - 2^{nd} paragraphs) treatment of spinal cord injuries and trauma is contemplated with the FGF-8 polypeptide. Spinal cord injuries and

[1] Claims 13-18 are cancelled in the present amendment.

injuries resulting from trauma almost always involve broken vertebrae and/or other broken bones, thus the treatment of bone disorders is encompassed by the disclosure of the WO 01/00662 document. In addition, because the claims fail to recite what the FGF-8 is effective for (see Rejections under 35 U.S.C. 112, second paragraph), the claims encompass administration of FGF-8, FGF-8 analog or FGF-8 agonist to anybody or anything for any purpose (pages 9-10).

This rejection is respectfully traversed. First of all, the claims, as amended, recite methods of administering FGF-8 or FGF-8 analogs in amounts effective to treat bone conditions associated with excessive resorption or breakdown of bone tissue, to increase or maintain bone density, or to treat osteoporosis, osteopenia, bone defects, or osteogenesis imperfecta. Thus, the claims disclose that the recited "effective amounts" of FGF-8 or agonists are effective for particular conditions.

Secondly, Singh does not disclose treatment of any of the conditions recited in Applicants' claims. Spinal cord injuries and injuries resulting from trauma do not "almost always involve broken vertebrae or other broken bones", as alleged in the Office Action. A spinal cord may be injured without a fracture being present, e.g., by dislocation without fracture, by interference with the blood supply, or by inflammatory or infective conditions, to name just a few. Bone fractures usually occur without spinal cord damage. An agent that may be of value in promoting healing of a spinal cord injury would not necessarily be expected to have any value in promoting healing of bone. Bone and neuronal tissues are completely different tissues. The types of neuronal damage contemplated by Singh as appropriate for treatment are unrelated to bone disorders. See Singh at page 8, line 20, to page 9, listing conditions such as trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, muscle injury, etc. as the types of neuronal damage suitable for treatment. Singh does not teach or suggest uses of FGF-8 and FGF-8 agonists for treatment of bone conditions. For at least the foregoing reasons, this rejection may be withdrawn.

Khodadoust, U.S. Pat. Pub. 20030022170

Claims 1, 3-7, 9-13, 15-18, and 21 were rejected under § 102(e) as anticipated by Khodadoust, U.S. Pat. Pub. 20030022170. The Office Action stated

> Khodadoust et al. teach the administration of a composition that has 98.6% similarity with SEQ ID NO:3 (see Appendix 2), or a fragment containing less than 50 amino acids of SEQ ID NO:3 (see [0012]) for "the purpose of stimulating chondrocyte growth thereby enhancing bone and periodontal regeneration..." (see [0323]). Evidence that the MFGF protein taught by Khodadoust et al. is closely related to FGF-8 can be found at [0358]...Thus the claims do not contribute anything over the prior art, particularly because Khodadoust et al. teach the administration of the polypeptides for the treatment of bone conditions (pages 10-11).

This rejection is respectfully traversed. Although Khodadoust discloses FGF-8, it does not teach use of FGF-8 or FGF-8 agonists in therapeutic methods, much less methods related to bone conditions recited in the present claims.

First of all, Khodadoust does not teach the administration of a composition that has 98.6% similarity with SEQ ID NO:3 in the methods recited in the claims. At paragraph [0323], Khodadoust states that "MFGF and MFGF therapeutics may also be employed to stimulate chondrocyte growth thereby enhancing bone and periodontal regeneration and aiding in tissue transplants or bone grafts." This is not a teaching to use FGF-8 or FGF-8 agonists as claimed. The "MFGF" polypeptides described by Khodadoust are <u>not</u> the same as FGF-8 polypeptides. Khodadoust describes MFGF polypeptides in paragraph [0006] as follows:

> The **newly identified proteins** and nucleic acids described herein are referred to as "MFGFs" and are exemplified here by both human and murine homologs of this gene. The human MFGF gene (herein referred to as hMFGF) transcript is shown in FIG. 1 (SEQ ID NO. 1) and includes 5' and 3' untranslated regions and a 621 base pair open reading frame (SEQ ID NO. 3) encoding a 207 amino acid polypeptide having **SEQ ID NO. 2**. The mature protein, i.e., the full length protein without the signal sequence is comprised of about 179 amino acids. Human MFGF is expressed predominantly in heart tissue. A nucleic acid comprising the cDNA encoding the full length human MFGF polypeptide was deposited at the American Type Culture Collection (12301 Parklawn Drive, Rockville, Md.) on Jan. 8, 1998 and has been assigned ATCC Designation No. 209574. The murine homolog of hMFGF has also been isolated and is herein referred to as mMFGF. The mMFGF gene transcript is shown in FIG. 2 (SEQ ID

> NO. 4) and includes 5' and 3' untranslated regions and a 621 bas pair open reading frame (SEQ ID NO. 6) encoding a 207 amino acid polypeptide having **SEQ ID NO. 5** (emphasis added).

See also paragraph [0057]:

> The terms "MFGF polypeptide" and "MFGF protein" are intended to encompass polypeptides comprising the amino acid sequence shown as SEQ ID NO. 2 or SEQ ID NO. 5 or fragments thereof, and homologs thereof and include agonist and antagonist polypeptides.

FGF-8 is not one of the "newly identified proteins" that Khodadoust discovered. Khodadoust discusses FGF-8 as a basis for comparison to MFGFs, not as a species of MFGF. It refers to FGF-8 and MFGFs as distinct polypeptides. The reference acknowledges that MGFs share homology with FGF-8, but does not teach uses of FGF-8. For example, paragraph [0363] states:

> This amino acid sequence alignment indicates that MFGF having **SEQ ID NO. 2** has the highest overall similarity to the human FGF-8 amino acid sequence and that it is about 60% identical and 75% similar to the amino acid sequence of human FGF-8. The cDNAs encoding human MFGF and FGF-8 (SEQ ID NO. 1) [sic, SEQ ID NO:11][2] have an overall identity of about 68% (emphasis added).

Although FGF-8 and MFGFs have similarities, Khodadoust does not teach that they are the same polypeptides.

Appendix 2 of the Office Action appears to present an alignment between SEQ ID NO:3 of the present application and SEQ ID NO:11 of Khodadoust. SEQ ID NO:11 of Khodadoust is a form of human FGF-8 (see paragraph [0362] of Khodadoust). Therefore, this alignment is not evidence of homology between Khodadoust's MFGFs and FGF-8. Rather, it is evidence of homology between one form of FGF-8 and another form of FGF-8. Khodadoust does not teach that one use SEQ ID NO:11 in therapeutic methods. Rather, the sequence is disclosed for the purposes of comparison with FGFs in Figure 3. The mere fact that Khodadoust discloses an

[2] Khodadoust erroneously referred to FGF-8 as "SEQ ID NO:1" in this paragraph. This appears to be a typographical error. Elsewhere, it states that SEQ ID NO:1 is the human MFGF gene transcript which encodes SEQ ID NO:2 (see paragraph [0006]), and it indicates that SEQ ID NO:11 corresponds to a human FGF-8 sequence (see paragraphs [0032], [0362], and Table III).

FGF-8 sequence does not mean that Khodadoust teaches its use. The focus of the methods in the publication are methods of using MFGFs. In view of the foregoing, Applicants respectfully request withdrawal of the rejection of the claims over this reference.

CONCLUSION

Allowance of the claims is respectfully requested in view of the above remarks. A Petition for Two-Month Extension of Time and the associated fee is being filed concurrently with this Amendment in Reply. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 08987-009001.

Respectfully submitted,

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